AVIAN INFLUENZA

Solving another piece of the H5N1 puzzle

As the H5N1 avian influenza virus continues to sweep across the globe, its potential to emerge as a human-adapted virus remains high. One crucial determinant of the species specificity of influenza viruses is the haemagglutinin (HA) protein: viruses carrying only 3 of the 16 known avian and mammalian HA subtypes (H1, H2 and H3) have adapted to humans, but in each case, these viruses have caused major pandemics.

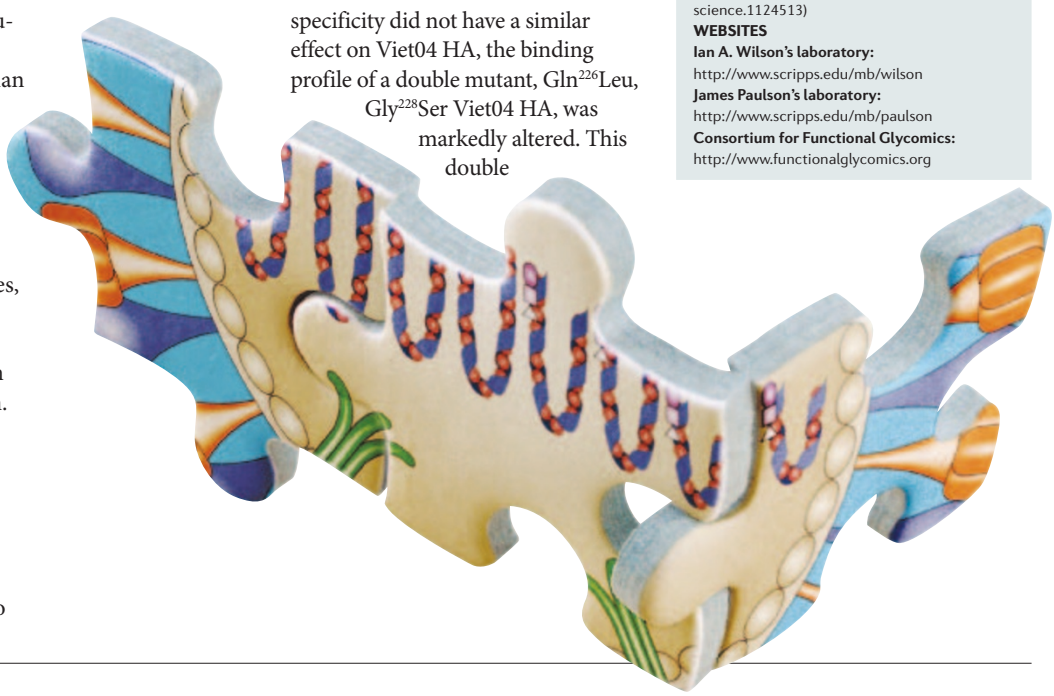
Stevens *et al.* now report the high-resolution crystal structure of the HA of a highly pathogenic H5N1 influenza virus (Viet04 HA). The study published in *Science* compares the Viet04 HA structure with an avian H5 HA structure (Sing97), and with HA structures from pandemic influenza A viruses — the deadly 1918 human H1 virus and the 1968 human H3 virus. In addition, the authors use new microarray technology to identify mutations that could allow H5N1 to take hold in the human population.

The general structure of Viet04 HA is similar to other HA structures, consisting of a globular head that contains the receptor-binding domain, a vestigial esterase domain and a membrane-proximal domain. Surprisingly, although the Viet04 HA sequence shows most similarity to that of the avian Sing97 HA, structural comparisons show that Viet04 HA is most closely related to the 1918 H1 HA. The crystal structure of 1918 HA0 revealed two pH-sensitive histidine patches, one in the membrane-proximal domain and one in the vestigial esterase domain, that are thought to promote release of the fusion peptide in the endosome, contributing to pathogenicity. The histidine patch in the membrane-proximal domain is conserved in Viet 04 HA, and additional structural features in the vestigial esterase might contribute further to virulence.

> “Surprisingly … Viet04 HA is most closely related to the 1918 H1 HA.”

Using glycan microarray technology, the authors showed that Viet04 HA binds preferentially to α2-3 sialic-acid glycan receptors, which typifies the binding specificity of avian influenza viruses. Although mutations in the receptor-binding domain that switch H3 HAs from avian to human specificity did not have a similar effect on Viet04 HA, the binding profile of a double mutant, $Gln^{226}Leu$, $Gly^{228}Ser$ Viet04 HA, was markedly altered. This double mutant showed reduced affinity for α2-3 receptors, with significant binding to a natural branched α2-6 biantennary glycan. The respiratory mucins in the human upper airway contain α2-3 glycans, which are thought to filter out avian virus that enters the respiratory tract. Reduced binding to these protective mucins coupled with enhanced binding to α2-6 biantennary glycans in the lower airways is one way in which H5N1 could establish a foothold in the human host.

Shannon Amoils



ORIGINAL RESEARCH PAPER Stevens, J. *et al.* Structure and receptor specificity of the hemagglutinin from an H5N1 influenza virus. *Science* 16 Mar 2006 (doi:10.1126/science.1124513)

WEBSITES

Ian A. Wilson's laboratory: http://www.scripps.edu/mb/wilson

James Paulson's laboratory: http://www.scripps.edu/mb/paulson

Consortium for Functional Glycomics: http://www.functionalglycomics.org